Purified Water	q.s*	--
Stearyl Alcohol	75.0	20
Talc	7.5	2
Magnesium Stearate	3.75	1
Total:	375.0	100

*Used in manufacture and remains in final product as residual quantity only.

The tablets of Example 1 are then tested for dissolution via the USP Basket Method, 37°C, 100 RPM, first hour 700 ml gastric fluid at pH 1.2, then changed to 900 ml at 7.5. The results are set forth in Table 2 below:

TABLE 2

Dissolution of Oxycodone 30 mg Controlled Release Tablets

Time	% Oxycodone Dissolved
1	33.1
2	43.5
4	58.2
8	73.2
12	81.8
18	85.8
24	89.2

EXAMPLE 2

Controlled Oxycodone HCl 10 mg Release Tablets - Organic Manufacture

The required quantities of oxycodone hydrochloride and spray dried lactose are transferred into an appropriate sized mixer and mix for approximately 6 minutes. Approximately 40 percent of the required Eudragit® RS PM powder is dispersed in Ethanol. While the powders are mixing, the powders are granulated with the dispersion and the mixing continued until a moist granular mass is formed. Additional ethanol is added if needed to reach granulation end point. The granulation is transferred to a fluid bed dryer and dried at 30°C; and then passed

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through a 12-mesh screen. The remaining Eudragit® RS PM is dispersed in a solvent of 90 parts ethanol and 10 parts purified water; and sprayed onto the granules in the fluid bed granulator/dryer at 30°C. Next, the granulate is passed through a 12-mesh screen. The required quantity of stearyl alcohol is melted at approximately 60-70°C. The warm granules are returned to the mixer. While mixing, the melted stearyl alcohol is added. The coated granules are removed from the mixer and allowed to cool. Thereafter, they are passed through a 12-mesh screen.

Next, the granulate is lubricated by mixing the required quantities of talc and magnesium stearate in a suitable blender. The granulate is then compressed to 125 mg tablets on a suitable tableting machine.

The formula for the tablets of Example 2 (10 mg controlled release oxycodone) is set forth in Table 3 below:

Table 3

Formula of Oxycodone HCl 10 mg Controlled Release Tablets

Component	Mg/Tablet	Percent (by wt)
Oxycodone hydrochloride	10.00	8
Lactose (spray-dried)	71.25	57
Eudragit® RS PM	15.00	12
Ethanol	q.s.*	--
Purified Water	q.s.*	--
Stearyl Alcohol	25.00	20
Talc	2.50	2
Magnesium stearate	1.25	1
Total:	125.00 mg	100

*Used only in the manufacture and remains in final product as residual quantity only.

The tablets of Example 2 are then tested for dissolution via USP Basket Method at 37°C, 100 RPM, first

hour 700 ml simulated gastric (pH 1.2) then changed to 900 ml at pH 7.5.

The results are set forth in Table 4 below:

Table 4

Dissolution of Oxycodone 10 mg
Controlled Release Tablets

Hour	% Dissolved
1	35.9
2	47.7
4	58.5
8	67.7
12	74.5
18	76.9
24	81.2

EXAMPLES 3 - 4

Controlled Release Oxycodone

10 and 20 mg Tablets (Aqueous Manufacture)

Eudragit® RS 30D and Triacetin® are combined while passing though a 60 mesh screen, and mixed under low shear for approximately 5 minutes or until a uniform dispersion is observed.

Next, suitable quantities of Oxycodone HCl, lactose, and povidone are placed into a fluid bed granulator/dryer (FBD) bowl, and the suspension sprayed onto the powder in the fluid bed. After spraying, the granulation is passed through a #12 screen if necessary to reduce lumps. The dry granulation is placed in a mixer.

In the meantime, the required amount of stearyl alcohol is melted at a temperature of approximately 70°C. The melted stearyl alcohol is incorporated into the granulation while mixing. The waxed granulation is transferred to a fluid bed granulator/dryer or trays and allowed to cool to room temperature or below. The cooled granulation is then passed through a #12 screen. There-

after, the waxed granulation is placed in a mixer/blender and lubricated with the required amounts of talc and magnesium stearate for approximately 3 minutes, and then the granulate is compressed into 125 mg tablets on a suitable tableting machine.

The formula for the tablets of Example 3 is set forth in Table 5 below:

Table 5

Formula of Controlled Release Oxycodone 10 mg Tablets

Component	Mg/Tablet	%(by wt)
Oxycodone Hydrochloride	10.0	8.0
Lactose (spray dried)	69.25	55.4
Povidone	5.0	4.0
Eudragit® RS 30D (solids)	10.0*	8.0
Triacetin®	2.0	1.6
Stearyl Alcohol	25.0	20.0
Talc	2.5	2.0
Magnesium Stearate	1.25	1.0
Total:	125.0	100.0

*Approximately 33.33 mg Eudragit® RS 30D Aqueous dispersion is equivalent to 10 mg of Eudragit® RS 30D dry substance.

The tablets of Example 3 are then tested for dissolution via the USP Basket Method at 37°C, 100 RPM, first hour 700 ml simulated gastric fluid at pH 1.2, then changed to 900 ml at pH 7.5. The results are set forth in Table 6 below:

Table 6

Dissolution of Oxycodone 10 mg Controlled Release Tablets

Hour	% Oxycodone Dissolved
1	38.0
2	47.5
4	62.0
8	79.8

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12	91.1
18	94.9
24	98.7

The formula for the tablets of Example 4 is set forth in Table 7 below:

Table 7

Formula of Controlled Release Oxycodone 20 mg Tablets

Component	Mg/Tablet
Oxycodone Hydrochloride	20.0
Lactose (spray dried)	59.25
Povidone	5.0
Eudragit® RS 30D (solids)	10.0*
Triacetin®	2.0
Stearyl Alcohol	25.0
Talc	2.5
Magnesium Stearate	1.25
Total:	125.0

The tablets of Example 4 are then tested for dissolution via the USP Basket Method at 37°C, 100 RPM, first hour 700 ml simulated gastric fluid at pH 1.2, then changed to 900 ml at pH 7.5. The results are set forth in Table 8 below:

Table 8

Dissolution of Oxycodone 20 mg Controlled Release Tablets

Hour	% Oxycodone Dissolved
1	31
2	44
4	57
8	71
12	79
18	86
24	89

EXAMPLES 5-6

In Example 5, 30 mg controlled release oxycodone hydrochloride tablets are prepared according to the process set forth in Example 1.

In Example 6, 10 mg controlled release oxycodone hydrochloride tablets are prepared according to the process set forth in Example 2.

Thereafter, dissolution studies of the tablets of Examples 5 and 6 are conducted at different pH levels, namely, pH 1.3, 4.56, 6.88 and 7.5.

The results are provided in Tables 9 and 10 below:

Table 9 - Example 5

Percentage Oxycodone HCl

30 mg Tablets Dissolved Over Time

pH	1	2	4	8	12	18	24
1.3	29.5	43.7	61.8	78.9	91.0	97.0	97.1
4.56	34.4	49.1	66.4	82.0	95.6	99.4	101.1
6.88	33.8	47.1	64.4	81.9	92.8	100.5	105.0
7.5	27.0	38.6	53.5	70.0	81.8	89.7	96.6

Table 10 - Example 6

Percentage Oxycodone HCl - 10 mg

Tablets Dissolved Over Time

pH	1	2	4	8	12	18	24
1.3	25.9	41.5	58.5	73.5	85.3	90.7	94.2
4.56	37.8	44.2	59.4	78.6	88.2	91.2	93.7
6.88	34.7	45.2	60.0	75.5	81.4	90.3	93.9
7.5	33.2	40.1	51.5	66.3	75.2	81.7	86.8

EXAMPLES 7-12

In Examples 7-12, 4 mg and 10 mg oxycodone HCl tablets were prepared according to the formulations and methods set forth in the assignee's U.S. Patent No. 4,990,341.

In Example 7, oxycodone hydrochloride (10.00 gm) was wet granulated with lactose monohydrate (417.5 gm) and hydroxyethyl cellulose (100.00 gm), and the granules were sieved through a 12 mesh screen. The granules were then dried in a fluid bed dryer at 50° C and sieved through a 16 mesh screen.

Molten cetostearyl alcohol (300.0 gm) was added to the warmed oxycodone containing granules, and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen.

Purified Talc (15.0 gm) and magnesium stearate (7.5 gm) were then added and mixed with the granules. The granules were then compressed into tablets.

Example 8 is prepared in the same manner as Example 7; however, the formulation includes 10 mg oxycodone HCl/tablet. The formulas for Examples 7 and 8 are set forth in Tables 11 and 12, respectively.

Table 11
Formulation of Example 7

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	10.0
Lactose monohydrate	167.0	417.5
Hydroxyethylcellulose	40.0	100.0
Cetostearyl alcohol	120.0	300.0
Purified talc	6.0	15.0
Magnesium stearate	3.0	7.5

Table 12
Formulation of Example 8

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	25.0
Lactose monohydrate	167.0	417.5
Hydroxyethylcellulose	40.0	100.0

Cetostearyl alcohol	120.0	300.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

In Example 9, 4 mg oxycodone HCl controlled release tablets are prepared according to the excipient formula cited in Example 2 of U.S. Patent No. 4,990,341. The method of manufacture is the same as set forth in Examples 7 and 8 above. Example 10 is prepared according to Example 9, except that 10 mg oxycodone HCl is included per tablet. The formulas for Examples 9 and 10 are set forth in Tables 13 and 14, respectively.

Table 13
Formulation of Example 9

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	10.0
Anhydrous Lactose	167.0	417.5
Hydroxyethylcellulose	30.0	75.0
Cetostearyl alcohol	90.0	225.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

Table 14
Formulation of Example 14

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	25.0
Hydrous lactose	167.0	417.5
Hydroxyethylcellulose	30.0	75.0
Cetostearyl alcohol	90.0	225.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

In Example 11, oxycodone 4 mg controlled release tablets are prepared with the same excipient formula cited in Example 3 of U.S. patent No. 4,990,341.

Oxycodone hydrochloride (32.0 gm) was wet granulated with lactose monohydrate (240.0 gm) hydroxyethyl cellulose (80.0 gm) and methacrylic acid copolymer (240.0 gm, Eudragit® L-100-55), and the granules were sieved through a 12 mesh screen. The granules were then dried in a Fluid Bed Dryer at 50° C and passed through a 16 mesh screen.

The warmed oxycodone containing granules was added molten cetostearyl alcohol (240.0 gm), and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen. The granules were then compressed into tablets.

Example 12 is prepared in identical fashion to Example 11, except that 10 mg oxycodone HCl is included per tablet. The formulations for Examples 11 and 12 are set forth in Tables 15 and 16, respectively.

Table 15

Formulation of Example 11

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	32.0
Lactose monohydrate	30.0	240.5
Hydroxyethylcellulose	10.0	80.0
Methacrylic acid copolymer	30.0	240.0
Cetostearyl alcohol	30.0	240.0

Table 16

Formulation of Example 12

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	80.0
Lactose monohydrate	30.0	240.5
Hydroxyethylcellulose	10.0	80.0
Methacrylic acid copolymer	30.0	240.0
Cetostearyl alcohol	30.0	240.0

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Next, dissolution studies were conducted on the tablets of Examples 7–12 using the USP basket method as described in the U.S. Pharmacopoeia XXII (1990). The speed was 100 rpm, the medium was simulated gastric fluid for the first hour followed by simulated intestinal fluid thereafter, at a temperature of 37° C. Results are given in Table 17.

TABLE 17

DISSOLUTION STUDIES OF EXAMPLES 7-12

Time	% Oxycodone Dissolved					
(hrs)	Ex. 7	Ex. 8	Ex. 9	Ex. 10	Ex. 11	Ex. 12
1	23.3	25.5	28.1	29.3	31.3	40.9
2	35.6	37.5	41.5	43.2	44.9	55.6
4	52.9	56.4	61.2	63.6	62.1	74.2
8	75.3	79.2	83.7	88.0	82.0	93.9
12	90.7	94.5	95.2	100.0	91.4	100.0

EXAMPLES 13–16

Clinical Studies

In Examples 13–16, randomized crossover bioavailability studies were conducted employing the formulation of Examples 2 (organic manufacture) and 3 (aqueous manufacture).

In Example 13, a single dose fast/fed study was conducted on 24 subjects with oxycodone tablets prepared according to Example 3.

In Example 14, a steady-state study was conducted on 23 subjects after 12 hours with oxycodone tablets prepared according to Example 2, and compared to a 5 mg oxycodone immediate-release solution.

In Example 15, a single dose study was conducted on 22 subjects using oxycodone tablets prepared according to Example 3, and compared to a 20 mg oxycodone immediate release solution.

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In Example 16, a 12 subject single-dose study was conducted using 3 x 10 mg oxycodone tablets prepared according to Example 3, and compared to a 30 mg oxycodone immediate release solution.

The results of Examples 13–16 are set forth in Table 18.

Table 18

Example	Dosage	AUC ng/ml/hr	Cmax ng/ml	Tmax hr
13	10 mg CR Fast	63	6.1	3.8
	10 mg CR Fed	68	7.1	3.6
14	5 mg IR q6h	121	17	1.2
	10 mg CR q12h	130	17	3.2
15	20 mg IR	188	40	1.4
	2 x 10 mg CR	197	18	2.6
16	30 mg IR	306	53	1.2
	3 x 10 mg CR	350	35	2.6
	30 mg CR	352	36	2.9

IR denotes immediate-release oxycodone solution.
CR denotes controlled-release tablets

EXAMPLE 17

CLINICAL STUDIES

In Example 17, a single dose, double blind, randomized study determined the relative analgesic efficacy, the acceptability, and relative duration of action of an oral administration of controlled release oxycodone 10, 20 and 30 mg prepared according to the present invention (CR OXY) compared to immediate release oxycodone 15 mg (IR OXY), immediate release oxycodone 10 mg in combination with acetaminophen 650 mg (IR OXY/APAP) and placebo in 180 patients with moderate or severe pain following abdominal or gynecological surgery. Patients rated their pain intensity and pain relief hourly for up to 12 hours postdosing. Treatments were compared using standard

scales for pain intensity and relief, and onset and duration of pain relief.

All active treatments were significantly superior to placebo for many of the hourly measures, and for sum pain intensity differences (SPID) and total pain relief (TOTPAR). A dose response was seen among the 3 dose levels of CR OXY for pain relief and peak pain intensity difference (PID), with CR OXY 20mg and 30 mg being significantly better than the 10 mg dose. IR OXY was significantly superior to CR OXY 10 mg at hr 1 and 2. IR OXY/APAP was significantly superior to the 3 doses of CR OXY at hr 1, and to CR OXY 10 mg at hrs 2 through 5. Onset time was significantly shorter for the IR OXY and IR OXY/APAP treatment groups in comparison to the 3 CR OXY treatments. The distribution functions for duration of relief revealed significantly longer duration of relief for the three CR OXY doses than for IR OXY and IR OXY/APAP. No serious adverse experiences were reported. The results are more particularly reported in Table 19 below.

TABLE 19

PATIENT DISPOSITION

TREATMENT GROUP

	IR OXY		-----CR OXY------				
	15mg	PLACEBO	10mg	20mg	30mg	2 PERC*	TOTAL
Enrolled and Randomized to Study Treatment	31	31	30	30	30	30	182
Entered the Study Treatment Phase	31	31	30	30	30	30	182
Completed the Study	31	30	30	30	30	30	181

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Discontinued from the Study	0	1	0	0	0	0	1
Excluded from Efficacy Analysis -Vomited prior to 1 hr post dose	0	1	0	0	0	0	1
-Inadvertently received rescue during study	1	0	0	0	0	0	1
Analysis Population: -Evaluable for Safety and Efficacy	30	30	30	30	30	30	180
-Evaluable for Safety	31	31	30	30	30	30	182

* 2 tablets of Percocet®

The time-effect curves for pain intensity, pain intensity differences and pain relief are shown in Figures 1-4. CR OXY 10 mg had significantly ($p < .05$) lower pain intensity scores than the placebo-treated patients at hours 3-11 and lower pain scores than IR OXY 15 mg and Percocet® at hour 10. CR OXY 20 mg has significantly ($p < .05$) lower pain intensity scores compared to placebo at hours 2 - 11 and significantly ($p < .05$) lower pain scores than CR OXY 10 mg, IR OXY 15 mg and Percocet at hours 9-11. CR OXY 30 mg had significantly ($p < .05$) lower pain scores than placebo at hours 2-11 and lower pain scores than CR OXY 10 mg at hours 2, 3, and 5 and lower scores than Percocet® at hour 10.

For hourly pain relief scores categorical and visual analog scales (CAT and VAS), CR OXY 10 mg had significantly ($p < .05$) higher pain relief scores than placebo at hours 3-11 and higher relief scores than IR OXY and Percocet® at hour 10 (and Percocet® at hour 11). CR OXY

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20 mg had significantly ($p < .05$) higher relief scores than placebo at hours 2-12 and higher relief scores than Percocet® at hours 9-12. In addition, CR OXY had significantly ($p < .05$) higher pain relief than IR OXY at hours 10-12. CR OXY 30 mg had significantly ($p < .05$) higher pain relief scores than placebo at hours 2-12 and higher scores than Percocet® at hours 9-12 and IR OXY 15 mg at hour 10.

Each treatment group was significantly ($p < .05$) better than placebo with respect to the sum of the pain intensity differences (SPID) and total pain relief (TOTPAR).

Duration of pain relief as measured by the patient stopwatch method showed that CR OXY 10 mg, 20 mg and 30 mg had significantly ($p < .05$) longer duration of action compared to IR OXY 15 mg and 2 tablets Percocet®. In addition, the three controlled-release formulations had significantly ($p < .05$) longer times to remedication compared to Percocet®.

Before remedication, a total of 104 (57%) of patients reported 120 adverse experiences. The most common were somnolence, fever, dizziness and headache.

Based upon the results of this study it is concluded that the controlled release oxycodone formulations of the present invention relieve moderate to severe post-operative pain, e.g., due to abdominal or gynecological surgery in women. There is a dose response noted in which placebo < 10 mg < 20 mg < 30 mg CR OXY following a single dose. Onset of action occurred in one hour with peak effects noted from 2 to 5 hours and a duration of effect from 10 to 12 hours. In the chronic pain situation steady state dosing may prolong this effect. Side effects are expected and easily managed. Headache may be related to dose. Dizziness and somnolence were reported.

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IR OXY 15 mg has an intermediate peak effect compared to controlled release oxycodone. Its duration of action is shorter (6-8 hours). Percocet® is quite effective in terms of onset, peak effect and safety. The duration of action is 6-8 hours.

In summary, CR OXY was clearly an effective oral analgesic, with a slower onset but a longer duration of effect than either IR OXY or IR OXY/APAP.

EXAMPLE 18

CLINICAL STUDIES

In Example 18, a steady state crossover trial was conducted in 21 normal male subjects comparing

a. CR OXY 10 mg administered every 12 hours (q12h); and

b. Roxicodone® oral solution 5 mg (ROX) administered every 6 hours (q6h),

Treatment (b) was the study reference standard. The average age was 34 years, height 176 cm and weight 75 kg. No unusual features were noted about the group.

Figure 5 shows the mean plasma oxycodone concentrations for the two formulations over the 12 hour dosing interval. The results are summarized in Table 18 in terms of mean values, ratios of mean values and 90% confidence intervals.

As inspection of Table 18 reveals, with one exception, no significant differences were detected between the two formulations. The single exception is the mean t_{max} for CR OXY of 3.18 hours which, as expected for a controlled release formulation, significantly exceeded the ROX mean of 1.38 hours. Mean AUC-based bioavailability, (ROX = 100%) was 104.4% with 90% confidence limits of 90.9 to 117.9%. Thus, the FDA specification of ±20% is met so that the study results support an assertion of equal oxycodone availability.

TABLE 20

SUMMARY OF PHARMACOKINETIC PARAMETERS FOR OXYCODONE FOLLOWING A SINGLE DOSE OF CR OXY (10mg q12H) AND ROXICODONE® ORAL SOLUTION (5mg q6h)

PARAMETER	CR OXY	ROXICODONE SOLUTION	OXY/ ROXI (%)	90% CI*
C_{max} (ng/mL)				
ARITH.MEAN(SD)	15.11(4.69)	15.57(4.41)	97.08	85.59-108.50
GEOMETRIC MEAN	14.43	15.01	95.14	
C_{6h} (ng/mL)				
ARITH.MEAN(SD)	6.24(2.64)	6.47(3.07)	96.41	80.15-112.74
GEOMETRIC MEAN	5.62	5.83	96.48	
t_{max} (hrs)				
ARITH.MEAN (SD)	3.18(2.21)	1.38(0.71)*	230.17	160.71-298.71
AUC(0-12 hrs)				
ARITH. MEAN(SD)	103.50(40.03)	99.10(35.04)	104.44	90.92-117.94
GEOMETRIC MEAN	97.06	93.97	103.29	
%Swing				
ARITH.MEAN (SD)	176.36(139.0)	179.0(124.25)	98.53	62.06-134.92
%Fluctuation				
ARITH. MEAN(SD)	108.69(38.77)	117.75 (52.47)	92.22	76.81-107.57
End Point				
ARITH. MEAN(SD)	-1.86(2.78)	-1.86(2.19)	99.97	117.77-22.23

*90% Confidence Interval
--Significant Difference p < 0.05

EXAMPLE 19

CLINICAL STUDIES

In Example 19, twenty-four normal, healthy male subjects were enrolled in a randomized single-dose two-way crossover study to compare the plasma oxycodone concentrations obtained after dosing with two controlled-release oxycodone 10 mg tablets versus 20 mg (20 ml of 5 mg/5 ml) of immediate release (IR) oxycodone hydrochloride solution. Twenty-three subjects completed the study and were eligible for analysis.

Plasma oxycodone concentrations were determined by a high performance liquid chromatographic procedure. Arithmetic Mean C_{max}, t_{max}, AUC, and half-lives calculated from individual plasma oxycodone concentration-versus-time data are set forth in Table 21:

TABLE 21

Pharmacokinetic Parameter	Reference Product IR Oxycodone 20 mg	Test Product CR Oxycodone 2 x 10 mg	F. (%)	90% Confidence Interval
C_{max} (ng/ml)	41.60	18.62	44.75	32.5-57.0
t_{max} (hours)	1.30	2.62	200.83	169.8-232.6
AUC (0-36) (mg x hr/ml)	194.35	199.62	102.71	89.5-115.9
AUC (0-∞) (ng x hr/ml)	194.38	208.93	107.49	92.9-121.9
$t_{½ (elim)}$ (hrs)	3.21	7.98*	249.15	219.0-278.8
$t_{½ (abs)}$ (hrs)	0.35	0.92*	264.17	216.0-310.7

F. % = Oral bioavailability
(CR oxycodone 2 x 10 mg/IR oxycodone 20 mg)
*Statistically significant (p = 0.0001)

For C_{max}, t_{max}, $t_{½ (elim)}$ and $t_{½ (abs)}$ there were statistically significant differences between the CR OXY and IR OXY. There were no statistically significant differences between the two treatments in the extent of absorption [AUC (0,36), AUC (0,∞). The 90% confidence

interval for CR OXY relative to IR OXY relative was 89.5% - 115.9% for AUC (0,36) and 92.9% - 121.9% for AUC (0,∞). Based on the 90% confidence interval analysis, the controlled-release oxycodone tablets were equivalent in extent of absorption (AUC 0,36) to the immediate-release oxycodone solution. The controlled-release oxycodone absorption was slower by approximately 1.3 hours. No statistically significant differences were noted between the two treatments with reference to adverse experiences, none of which were considered clinically unusual for opiates for this type of study.

The above studies demonstrate a significant dose-response relationship utilizing the controlled release oxycodone formulations of the present invention at dosages of 10, 20 and 30 mg which does not deviate from parallelism with dose-response slopes for MS Contin in similarly designed well-controlled analgesic efficacy studies of MS Contin reported by Kaiko R.S., Van Wagoner D., Brown J., et al., "Controlled-Release Oral Morphine (MS Contin® Tablets, MSC) in Postoperative Pain.", Pain Suppl., 5:S149 1990, who compared 30, 60, 90, and 120 mg of MS Contin as compared with 10 mg of intramuscular morphine and placebo and Bloomfield, et al., "Analgesic Efficacy and Potency of Two Oral Controlled-Release Morphine Preparations", Clinical Pharmacology & Therapeutics, (in press), who compared 30 and 90 mg of MS Contin as compared to 30 and 90 mg of another controlled-release oral morphine preparation, Oramorph SR 30 mg tablets.

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method for substantially reducing the range in daily dosages required to control pain in human patients, comprising administering an oral controlled release dosage formulation comprising from about 10 to about 40 mg oxycodone or a salt thereof which provides a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

2. A method for substantially reducing the range in daily dosages required to control pain in substantially all human patients, comprising administering an oral solid controlled release dosage formulation comprising from about 10 mg to about 160 mg oxycodone or a salt thereof which provides a mean maximum plasma concentration of oxycodone up to about 240 ng/ml from a mean of up to about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration up to about 120 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

3. A controlled release oxycodone formulation for oral administration to human patients, comprising from about 10 to about 40 mg oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after

repeated administration every 12 hours through steady-state conditions.

4. A controlled release oxycodone formulation for oral administration to human patients, comprising from about 10 mg to about 160 mg oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 120 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

5. A solid controlled release oral dosage form, comprising

(a) oxycodone or a salt thereof in an amount from about 10 to about 160 mg;

(b) an effective amount of a controlled release matrix selected from the group consisting of hydrophilic polymers, hydrophobic polymers, digestible substituted or unsubstituted hydrocarbons having from about 8 to about 50 carbon atoms, polyalkylene glycols, and mixtures of any of the foregoing; and

(c) a suitable amount of a suitable pharmaceutical diluent, wherein said composition provides a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 120 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

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..J/US 20 JAN 1993

6. The controlled release composition of claim 5, wherein said controlled release matrix comprises an acrylic resin.

7. A solid controlled release oral dosage form, comprising

(a) an analgesically effective amount of spheroids comprising oxycodone or a salt thereof and either a spheronising agent or an acrylic polymer or copolymer, such that the total dosage of oxycodone in said dosage form is from about 10 to about 160 mg;

(b) a film coating which controls the release of the oxycodone or oxycodone salt at a controlled rate in an aqueous medium, wherein said composition provides an in vitro dissolution rate of the dosage form;

said composition providing a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

8. The controlled release composition of claim 7, wherein said film coating comprises a water insoluble material selected from the group consisting of shellac or zein, a water insoluble cellulose, or a polymethacrylate.

9. A controlled release tablet for oral administration comprising from about 10 to about 160 mg oxycodone or an oxycodone salt dispersed in a controlled release matrix, said tablet providing an in-vitro dissolution of the dosage form, when measured by the USP Paddle Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C, between 12.5% and 42.5%

(by wt) oxycodone released after 1 hour, between 25% and 55% (by wt) oxycodone released after 2 hours, between 45% and 75% (by wt) oxycodone released after 4 hours and between 55% and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being substantially independent of pH and chosen such that a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml is obtained in vivo from a mean of about 2 to about 4.5 hours after administration of the dosage form, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

10. A dosage form according to claim 9, wherein the in vitro dissolution rate is between 17.5% and 38% (by wt) oxycodone released after 1 hour, between 30% and 50% (by wt) oxycodone released after 2 hours, between 50% and 70% (by wt) oxycodone released after 4 hours and between 60% and 80% (by wt) oxycodone released after 6 hours.

11. A dosage form according to claim 9, wherein the in vitro dissolution rate is between 17.5% and 32.5% (by wt) oxycodone released after 1 hour, between 35% and 45% (by wt) oxycodone released after 2 hours, between 55% and 65% (by wt) oxycodone released after 4 hours and between 65% and 75% (by wt) oxycodone released after 6 hours.

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RO/US 20 JAN 1993

ABSTRACT OF THE DISCLOSURE

A method for substantially reducing the range in daily dosages required to control pain in approximately 90% of patients is disclosed whereby an oral solid controlled release dosage formulation having from about 10 to about 40 mg of oxycodone or a salt thereof is administered to a patient. The formulation provides a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions. Another embodiment is directed to a method for substantially reducing the range in daily dosages required to control pain in substantially all patients by administering an oral solid controlled release dosage formulation comprising up to about 160 mg of oxycodone or a salt thereof, such that a mean maximum plasma concentration of oxycodone up to about 240 ng/ml from a mean of up to about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration up to about 120 ng/ml from about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions are achieved. Controlled release oxycodone formulations for achieving the above are also disclosed.

92-515

PATENT COOPERATION TREATY

APPOINTMENT OF AGENT OR COMMON REPRESENTATIVE

The undersigned applicant hereby appoints as agents:
Clifford M. Davidson, Harold D. Steinberg,
Martin G. Raskin, and Brian Roffe of
STEINBERG & RASKIN
1140 Avenue of the Americas
New York, N.Y. USA 10036
to act on its behalf before the competent International Authorities in connection with the following international application:

TITLE: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

INTERNATIONAL APPLICATION NO.: PCT/US92/10146

INTERNATIONAL FILING DATE : November 25, 1992

filed with the United States Receiving Office and to receive payments on its behalf.

APPLICANT: Euroceltique S.A.
15 East 62nd Street
New York, New York 10021
Unites States of America

INVENTOR/ APPLICANT: Benjamin OSHLACK

ADDRESS: 351 East 84th Street, New York, New York 10028

SIGNATURE: Benjamin Oshlack

DATE: January 6th 1993

INVENTOR/ APPLICANT: Mark CHASIN

ADDRESS: 3 Wayne Court, Manalpan, New Jersey 07726

SIGNATURE: Mark Chasin

DATE: January 6, 1993

PTO/US 92/10146
..J/US 20 JAN 1993

INVENTOR/ APPLICANT:	John Joseph MINOGUE
ADDRESS:	4 Woodside Drive, New City, New York 10956
SIGNATURE:	John Joseph Minogue
DATE:	1-8-93
INVENTOR/ APPLICANT:	Robert KAIKO
ADDRESS:	10 Norfield Woods Rd., Weston, Connecticut 06883
SIGNATURE:	
DATE:	1/12/93

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'912 - 85

08/081302

FORM PTO-1595
1-31-92

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

RECORDATION FORM COVER SHEET
PATENTS ONLY

39 Rec'd PCT/PTO 18 JUN '93

Tab settings ⇩ ⇩⇩

To the Honorable Commissioner of Patents and Trademarks. Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Benjamin OSHLACK, Mark CHASIN,
John Joseph MINOGUE, and
Robert Francis KAIKO
Additional name(s) of conveying party(ies) attached? ☐ yes ☒ no

2. Name and address of receiving party(ies): A/D
Name: EUROCELTIQUE, S.A.
Internal Address:
Street Address: 122 Boulevard de la Petrusse
City: Luxembourg State: ZIP
Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of Conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other
Execution Date: May 14, 1993

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is: May 14, 1993
A. Patent Application No.(s)
B. Patent No.(s)
Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:
Name: Steinberg & Raskin
Internal Address: 93-311
Street Address: 1140 Avenue of the Americas
City: New York State: NY ZIP 10036

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41): $ 40.00
☒ Enclosed
☐ Authorized to be changed to deposit account

8. Deposit account number:
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Harold D. Steinberg
Name of Person Signing
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Signature
June 18, 1993
Date
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OMB No. 0651-0011 (exp. 4/94)

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6717 0689

'912 - 86

93-311

Assignment of Application for Patent

Whereas, Benjamin OSHLACK, Mark CHASIN, John Joseph MINOGUE and Robert Francis Kaiko, respectively

of 351 East 84th St., New York, NY 10028, 3 Wayne Court, Manalpan, NJ 07726, 33 E. Grand St., B-2B Mount Vernon, NY 10552 and 10 Norfield Woods Rd., Weston, CT 06883 have invented certain new and useful improvements in Controlled Release Oxycodone Compositions (Title of Invention)

for which they are about to make (He has made—or is about to make.) application for Letters Patent of the United States of America:

And Whereas, EUROCELTIQUE, S.A.

of 122 Boulevard de la Petrusse, Luxembourg, desirous of acquiring an interest therein and in the Letters Patent to be obtained therefor from the United States;

Now Therefore, be it known by all whom it may concern, that for and in consideration of one Dollars ($ 1.00) and other valuable consideration to us in hand paid, the receipt of which is hereby acknowledged we have assigned, sold, and set over, and by these presents do assign, sell, and set over unto the said EUROCELTIQUE, S.A.

~~for the territory of the United States of America, and for all foreign countries~~

† for the territory of the United States of America, and for all foreign countries

* all right, title, and interest in and to the said invention, as fully set forth and described in the specification prepared and executed by us on May 14 19 93 filed 19, serial No., preparatory to obtaining Letters Patent therefor; said invention, application and Letters Patent to be held and enjoyed by the said EUROCELTIQUE, S.A. for its own use and behoof, ~~and for~~

to the full end of the term for which said Letters Patent are granted, as fully and entirely as the same would have been held by us had this assignment and sale not been made.

RECORDED
PATENT & TRADEMARK OFFICE
JUN 18 93

Benjamin OSHLACK

John Joseph MINOGUE

(Inventor's full signature.) Mark CHASIN

Robert Francis KAIKO

† Either one of these lines MUST be cancelled.
* State whether the full and exclusive right, or what part of the whole interest is assigned.

Dated: 14th May 1993

6717 0690

'912 - 87

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O.G. FIG. | CLASS | SUBCLASS | APPROVED BY DRAFTSMAN

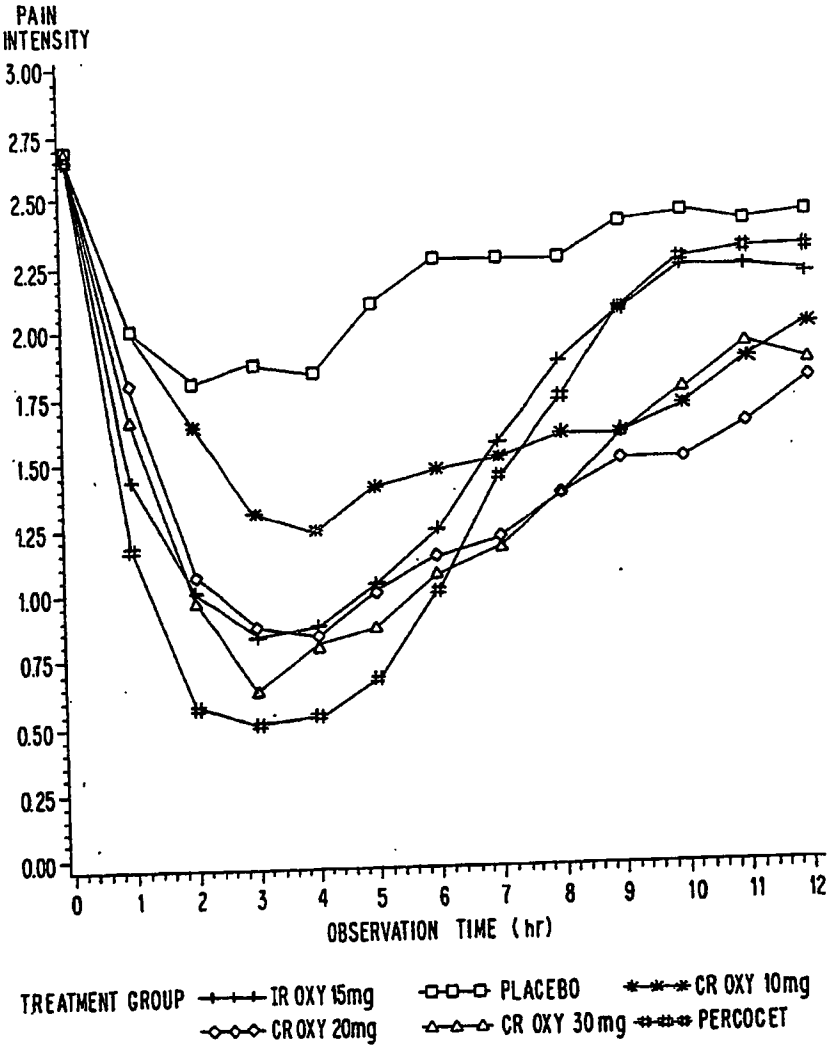

FIG. 1

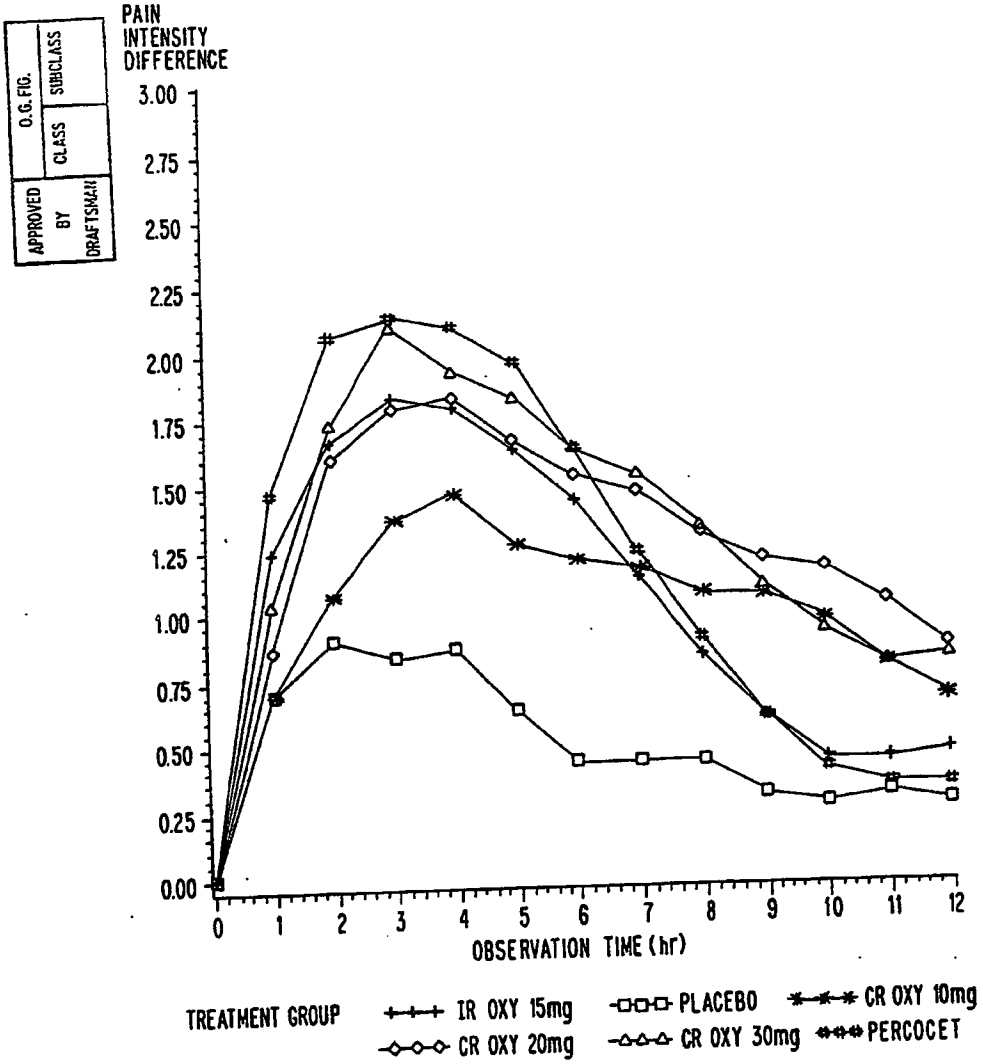

FIG.2

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O.G. FIG. | CLASS | SUBCLASS
APPROVED BY DRAFTSMAN

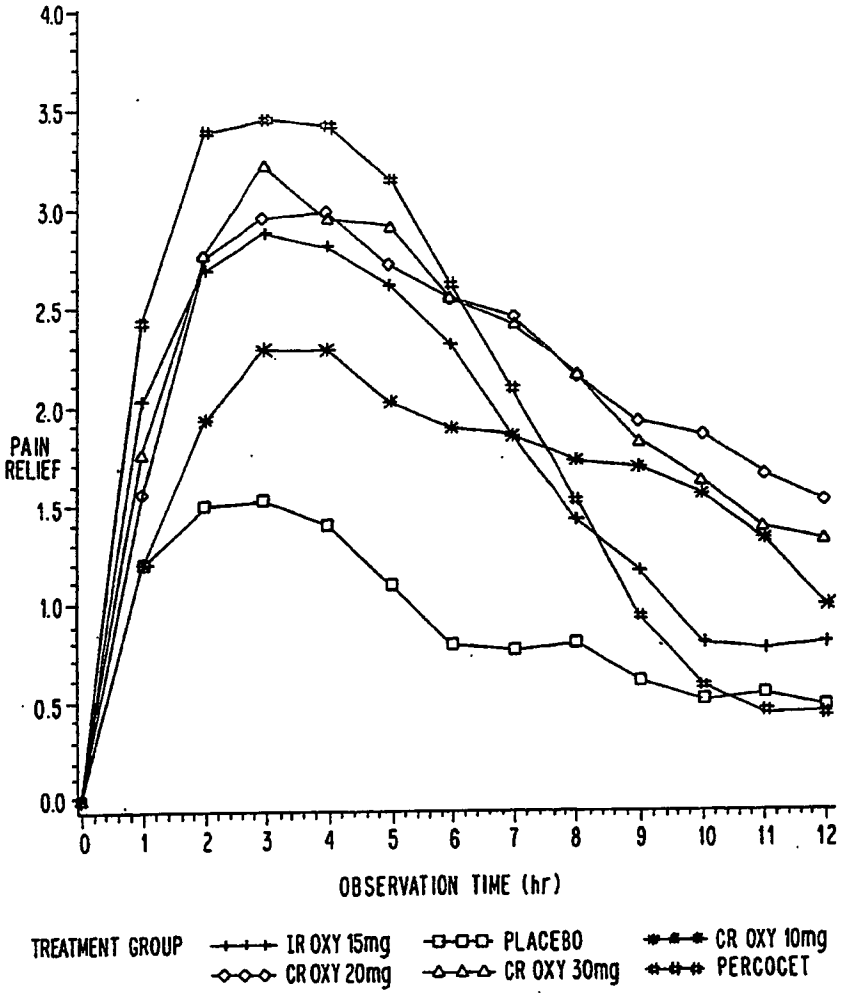

FIG. 3

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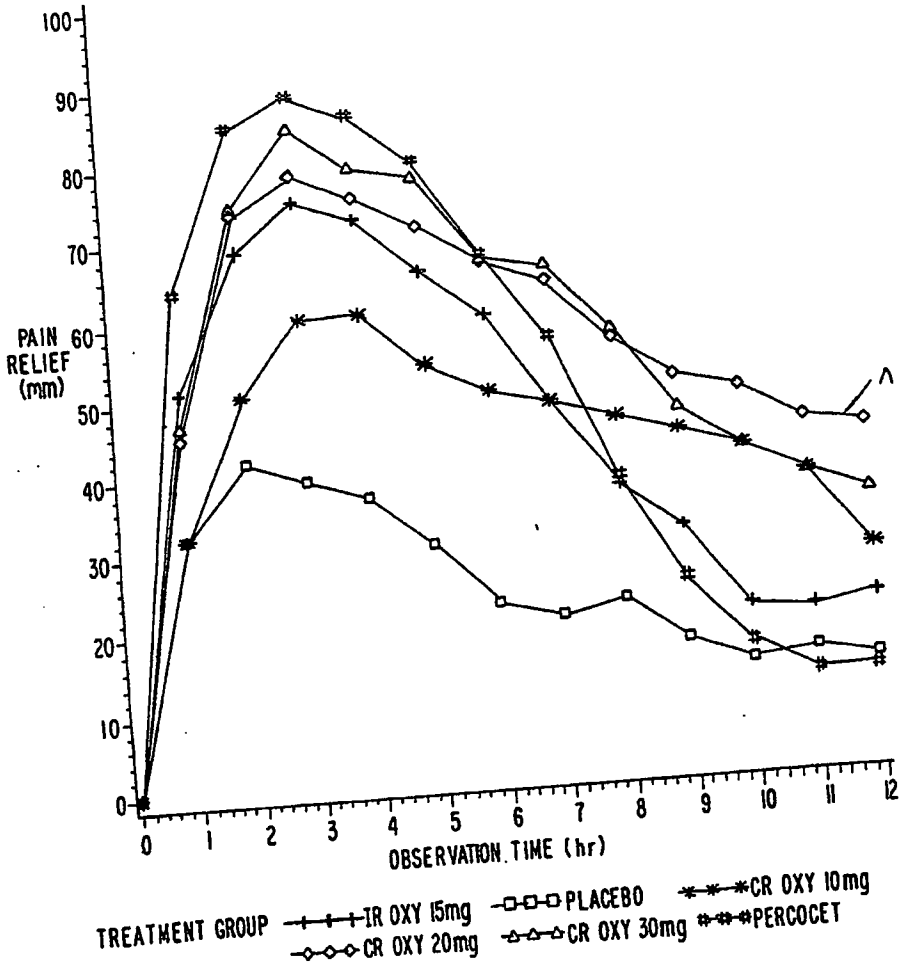

FIG. 4

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APPROVED BY DRAFTSMAN	O.G. FIG. CLASS	SUBCLASS

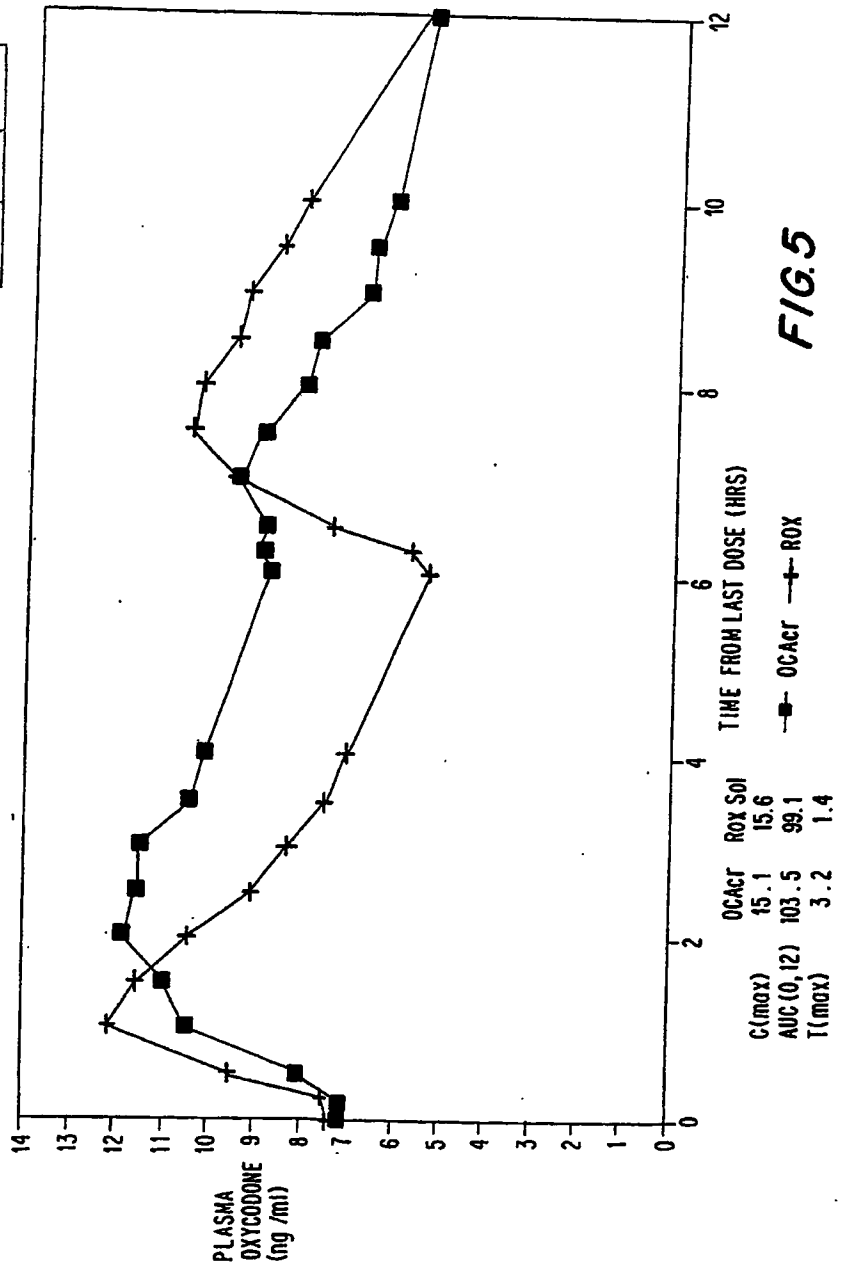

FIG.5

'912 - 92

93-311

UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	Application of:	Benjamin OSHLACK et al.
	Serial No.:	Not Yet Known
	Filed:	Simultaneously
	For:	CONTROLLED RELEASE OXYCODONE COMPOSITIONS

LETTER RE: PRIORITY

Hon. Commissioner of Patents and Trademarks June 18, 1993

Washington, D.C. 20231

Sir:

Applicants hereby claim, through International Application No. PCT/US92/10146 filed November 25, 1992, the priority of United States Patent Application Serial No. 07/800,549 filed November 27, 1991.

Respectfully Submitted,

STEINBERG AND RASKIN

By: _____
Harold D. Steinberg
Reg. No. 17,255
(212) 768-3800

"Express Mail" mailing label no. RB 832 223 876 US
Date of Deposit: JUNE 18, 1993
I hereby certify that this correspondence and/or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above, in an envelope addressed to: "Commissioner of Patents and Trademarks, Washington, DC 20231".

STEINBERG & RASKIN

By: Naomi Graham
Da

'912 - 93

93-311 #2

UNITED STATES PATENT AND TRADEMARK OFFICE

Re: Application of: Benjamin OSHLACK et al.

Serial No.: 08/081,302

Filed: June 18, 1993

For: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

INFORMATION DISCLOSURE STATEMENT

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

August 24, 1993

Sir:

Applicants hereby submit PTO form 1449 which lists references cited during the prosecution of the priority application, U.S. Serial No. 07/800,549 filed November 27, 1991. Copies of the references are enclosed.

This Information Disclosure Statement is being filed within three months from the filing date of the present application. Therefore, no fee is due under 37 C.F.R. §1.17(p).

It is respectfully requested that these references be considered and made of record.

Respectfully submitted,

STEINBERG & RASKIN

By: _____
Clifford M. Davidson
Reg. No. 32,728

Steinberg & Raskin
1140 Avenue of the Americas
New York, New York 10036
(212) 768-3800

Enclosures
PTO-1449
2 References

I hereby certify that this correspondence and/or fee is being deposited with the United States Postal Service as first class mail in an envelope addressed to "Commissioner of Patents and Trademarks, Washington, DC 20231" on August 24, 1993.

STEINBERG & RASKIN

BY: _____

'912 - 94

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PATENT AND TRADEMARK OFFICE

Sheet 1 of 1

ATTY. DOCKET NO. 93-311

SERIAL NO. 08/081,302

APPLICANT Benjamin OSHLACK et al.

FILING DATE June 18, 1993

GROUP 1502

LIST OF PRIOR ART CITED BY APPLICANT

(Use several sheets if necessary)

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIAT
	AA	4 8 6 1 5 9 8	8/89	Oshlack	424	470	
	AB	4 9 9 0 3 4 1	2/91	Goldie et al.	424	484	
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AL							
	AM							
	AN							
	AO							
	AP							

OTHER PRIOR ART *(Including Author, Title, Date, Pertinent Pages, Etc.)*

	AR		
	AS		
	AT		

EXAMINER

DATE CONSIDERED 8/94

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

USCOMM-DC 80-3885

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UNITED STATES DEPARTMENT OF COMMERCE
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Washington, D.C. 20231

#3

US APPLICATION NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/081,302	OSHLACK	B 93-311

5621

HAROLD D. STEINBERG
STEINBERG & RASKIN
1140 AVENUE OF THE AMERICAS
NEW YORK, NEW YORK 10036

PCT/US92/10146
INTERNATIONAL APPLICATION NO.

11/25/92 11/27/91
I.A. FILING DATE PRIORITY DATE
10/04/93

DATE MAILED:

NOTIFICATION OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C. 371 AND 37 CFR 1.494 OR 1.495

1. The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as ☑ a Designated Office (37 CFR 1.494), ☐ an Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is **ACCEPTED** for national patentability examination in the United States Patent and Trademark Office.

2. The United States Application Number assigned to the application is shown above and the relevant dates are:

JUN 18 1993	JUN 18 1993
35 U.S.C. 102(e) DATE	DATE OF RECEIPT OF 35 U.S.C. 371 REQUIREMENTS

3. ☐ A request for immediate examination under 35 U.S.C. 371(f) was received on _____ and the application will be examined in turn.

4. The following items have been received:
- ☑ U.S. Basic National Fee.
- ☑ Copy of the international application in:
  - ☐ a non-English language.
  - ☑ English.
- ☑ Translation of the international application into English.
- ☑ Oath or Declaration of inventors(s) for DO/EO/US.
- ☐ Copy of Article 19 amendments. ☐ Translation of Article 19 amendments into English.
  The Article 19 amendments ☐ have ☐ have not been entered.
- ☐ The International Preliminary Examination Report in English and its Annexes, if any.
- ☐ Translation of Annexes to the International Preliminary Examination Report into English.
  The Annexes ☐ have ☐ have not been entered.
- ☐ Preliminary amendment(s) filed _____ and _____.
- ☑ Information Disclosure Statement(s) filed AUG 26 1993 and _____.
- ☑ Assignment document.
- ☐ Power of Attorney and /or Change of Address.
- ☐ Substitute specification filed _____.
- ☐ Verified Statement Claiming Small Entity Status.
- ☐ Priority Document.
- ☐ Copy of the Search Report ☐ and copies of the references cited therein.
- ☐ Other:

A Filing Receipt (PTO-103X) will be issued for the present application in due course. Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

Applicant is reminded that any communication to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above. (37 CFR 1.5)

Paulette LeCuell
Telephone: (703) 305-3163

FORM PCT/DO/EO/903 (May 1993)

'912 - 96

U.S. Appl. No. 08/081502 **DO/US WORKSHEET** International Appl No. US92/10141

Application filed by: ☑ 20 months ☐ 30 months

INTERNATIONAL APPLICATION PAPERS IN THE APPLICATION FILE:

- ☑ International application (RECORD COPY)
- ☐ Article 19 amendments
- ☐ PCT/IB/331
- ☐ PCT/IPEA/409 IPER (PCT/IPEA/416 on front)
- ☐ Annexes to 409
- ☐ Priority document(s) No._____
- ☐ INTERNATIONAL APPLICATION ON DOUBLE SIDED PAPER (COPIES MADE)
- ☑ Request form PCT/RO/101
- ☐ PCT/IB/302
- ☐ PCT/ISA/210-Search Report
- ☐ Search Report references
- ☐ Other _____

RECEIPTS FROM THE APPLICANT: (other than checked above)

- ☑ Basic National Fee (paid or authorized to charge)
- Translation of international application as filed:
  - ☑ Description
  - ☐ Claims
  - ☐ Words in the drawing figure(s)
  - ☐ Article 19 amendments
  - ☐ Annexes to 409
- ☑ Oath / Declaration
- ☐ DNA diskette
- ☐ Preliminary amendment(s) filed
- ☐ _____
- ☐ _____
- ☑ Assignment document
- ☐ Power of attorney/Change of address
- ☐ Substitute specification
- ☐ Verified small status claim
- ☐ Other _____

Notes:

35 U.S.C. 371 - Receipt of Request (PTO-1390)	JUN 18 1993
Date acceptable oath / declaration received	
Date complete 35 U.S.C 371 requirements met	JUN 18 1993
102(e) Date	
Date of completion of DO/EO 906 - Notification of Missing 102(e) Requirements	
Date of completion of DO/EO 907 - Notification of Acceptance for 102(e) date	
Date of completion of DO/EO 911 - Application accepted under 35 U.S.C. 1.11	
Date of completion of DO/EO 905 - Notification of Missing Requirements	
Date of completion of DO/EO 916 - Notification of Defective Response	
Date of completion of DO/EO 903 - Notification of Acceptance	
Date of completion of DO/EO 909 - Notification of Abandonment	

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Publication No.
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Publication Date
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Publication Language
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Not Published
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Designated
☐ EP request

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May 1993

'912 - 97

DO/EO BIBLIOGRAPHIC DATA ENTRY

SERIAL NUMBER: 08 / 081302
IA NUMBER: PCT/ US92 / 10146
FAMILY NAME: OSHLACK
GIVEN NAME: BENJAMIN
PRIORITY CLAIMED (Y/N): Y
NO BASIC FEE (Y/N); N
ATTORNEY DOCKET NUMBER: 93-311
CORRESPONDENTS NAME/ADDRESS:
HAROLD D. STEINBERG
STEINBERG & RASKIN
1140 AVENUE OF THE AMERICAS
NEW YORK, NEW YORK 10036

RECEIPT DATE: 06 / 18 / 93
IA FILING DATE: 11 / 25 / 92
DELAY WAIVED (Y/N): Y
DEMAND RECEIVED (Y/N): N
PRIORITY DATE: 11 / 27 / 91
US DESIGNATED ONLY (Y/N): N
COUNTRY: USX

APPLICATION TITLES:
CONTROLLED RELEASE OXYCODONE COMPOSITIONS

OK TO UPDATE? (Y OR N) Y

'912 - 98

A61K

(21) Int. Application Number: PCT/US92/10146
(22) Int. Filing Date: 25 November 1992 (25.11.92)
(30) Priority data: 800,549 27 November 1991 (27.11.91) US

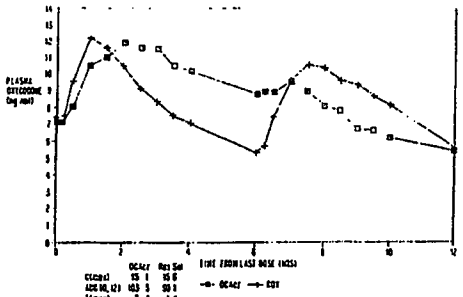
(71) Applicant (for all designated States except US): EUROCELTIQUE S.A. [US/US]; 15 East 62nd Street, New York, NY 10021 (US).
(72) Inventors; and
(75) Inventors/Applicants (for US only): OSHLACK, Benjamin [US/US]; 351 East 84th Street, New York, NY 10028 (US). CHASIN, Mark [US/US]; 3 Wayne Court, Manalpan, NJ 07726 (US). MINOGUE, John, Joseph [US/US]; 33 East Grand Street, B-2B, Mount Vernon, NY 10552 (US). KAIKO, Robert, Francis [US/US]; 10 Norfield Woods Road, Weston, CT 06883 (US).
(74) Agents: STEINBERG, Harold, D. et al.; Steinberg and Raskin, 1140 Avenue of the Americas, New York, NY 10036 (US).

(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, PT, RO, RU, SD, SE, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
With international search report.

(51) International Patent Classification 5: A61K 9/22
A1
(11) Int. Publication Number: WO 93/10765
(43) Int. Publication Date: 10 June 1993 (10.06.93)

(54) Title: CONTROLLED RELEASE OXYCODONE COMPOSITIONS



(57) Abstract

A method for substantially reducing the range in daily dosages required to control pain in approximately 80 % of patients is disclosed whereby an oral solid controlled release dosage formulation having from about 10 to about 40 mg of oxycodone or a salt thereof is administered to a patient. The formulation provides a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hours) administration through steady-state conditions. Another embodiment is directed to a method for substantially reducing the range in daily dosages required to control pain in substantially all patients. The figure is a graph showing the mean plasma oxycodone concentration for a 10 mg controlled release oxycodone formulation prepared in accordance with the present invention and a study reference standard.

(21) Int. Application Number: PCT/DE92/01008
(22) Int. Filing Date: 4 December 1992 (04.12.92)
(30) Priority data: P 41 40 184.0 5 December 1991 (05.12.91) DE

(71) Applicants (for all designated States except US): ALFATEC-PHARMA GMBH [DE/DE]; Im Neuenheimer Feld 519, D-6900 Heidelberg (DE). PAZ ARZNEIMITTELENTWICKLUNGSGESELLSCHAFT MBH [DE/DE]; In der Schildwacht 13, D-6230 Frankfurt/Main 80 (DE).
(72) Inventors; and
(75) Inventors/Applicants (for US only): WUNDERLICH, Jens-Christian [DE/DE]; Bothestraße 52, D-6900 Heidelberg (DE). SCHUSTER, Otto [DE/DE]; Kelkheimerstraße 69, D-6232 Bad Soden (DE). LUKAS, Helmut [DE/DE]; Taunusstraße 30, D-6078 Neu-Isenburg (DE). SCHICK, Ursula [DE/DE]; Stadtbahnhofstraße 6, D-6908 Wiesloch (DE).
(74) Agent: KUHNEN, WACKER & PARTNER; Alois-Steinecker-Str. 22, Postfach 1553, D-8050 Freising (DE).

(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

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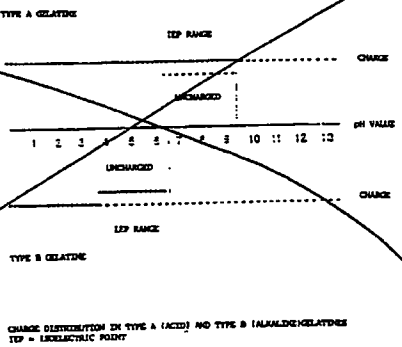
A1
(11) Int. Publication Number: WO 93/10766
(43) Int. Publication Date: 10 June 1993 (10.06.93)

(54) Title: IMMEDIATE-EFFECT FLURBIPROFEN-CONTAINING MEDICAMENT AND ITS USE



(57) Abstract

A medicament for immediately treating painful, inflammatory and/or febrile acute diseases contains flurbiprofen as a racemate, a mixture of a racemate with its enantiomers, a pseudoracemate (mixtures of equal parts of S- and R-flurbiprofen) or as a mixture of different parts of S- and R-flurbiprofen in the range extending between pure S- and pure R-flurbiprofen as active substance in the form of a pharmaceutically applicable nanosol. This medicament satisfies all requirements of an immediate-effect pharmaceutic form.

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RO/

INTERNATIONAL APPLICATION UNDER THE PATENT COOPERATION TREATY

REQUEST

THE UNDERSIGNED REQUESTS THAT THE PRESENT INTERNATIONAL APPLICATION BE PROCESSED ACCORDING TO THE PATENT COOPERATION TREATY

(The following is [illegible] Office)
INTERNATIONAL APPLICATION No.: PCT/US92/10146
INTERNATIONAL FILING DATE: 25 NOV 1992
(Stamp) Name of receiving Office: PCT INTERNATIONAL APPLICATION ROUTING
Applicant's or agent's file reference (indicated by applicant if desired): 92-515

Box No. I TITLE OF INVENTION

Controlled Release Oxycodone Compositions

Box No. II APPLICANT (WHETHER OR NOT ALSO INVENTOR); DESIGNATED STATES FOR WHICH HE/SHE/IT IS APPLICANT. Use this box for indicating the applicant or, if there are several applicants, one of them. If more than one person (includes, where applicable, a legal entity) is involved, continue in Box No. III.

The person identified in this box is (mark one check-box only): ☐ applicant and inventor* ☒ applicant only

Name and address:** Euroceltique S.A.
15 East 62nd Street
New York, New York 10021
United States of America

Telephone number (including area code): 212-032-7900
Telegraphic address:
Teleprinter address:

State of nationality: US
State of residence:*

The person identified in this box is applicant for the purposes of (mark one check-box only):
☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the "Supplemental Box"

Box No. III FURTHER APPLICANTS, IF ANY; (FURTHER) INVENTORS, IF ANY; DESIGNATED STATES FOR WHICH THEY ARE APPLICANTS (IF APPLICABLE). A separate sub-box has to be filled in in respect of each person (includes, where applicable, a legal entity). If the following two sub-boxes are insufficient, continue in the "Supplemental Box," (giving there for each additional person the same indications as those requested in the following two sub-boxes) or by using a "continuation sheet."

The person identified in this sub-box is (mark one check-box only): ☒ applicant and inventor* ☐ applicant only ☒ inventor only*

Name and address:** OSHLACK, Benjamin
351 East 84th Street
New York, New York, United States of America 10028

If the person identified in this sub-box is applicant (or applicant and inventor), indicate also:

State of nationality: US State of residence:* US

and whether that person is applicant for the purposes of (mark one check-box only):
☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the "Supplemental Box"

The person identified in this sub-box is (mark one check-box only): ☒ applicant and inventor* ☐ applicant only ☒ inventor only*

Name and address:** CHASIN, Mark
3 Wayne Court
Manalpan, New Jersey United States of America 07726

If the person identified in this sub-box is applicant (or applicant and inventor), indicate also:

State of nationality: US State of residence:* US

and whether that person is applicant for the purposes of (mark one check-box only):
☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the "Supplemental Box"

* If the person indicated as "applicant and inventor" or as "inventor only" is not an inventor for the purposes of all the designated States, give the necessary indications in the "Supplemental Box."

** Indicate the name of a natural person by giving his/her family name first followed by the given name(s). Indicate the name of a legal entity by its full official designation. In the address, include both the postal code (if any) and the State (name).

*** If residence is not indicated, it will be assumed that the State of residence is the same as the State indicated in the address.

Form PCT/RO/101 (first sheet) (January 1991) See notes on accompanying sheet

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THIS SHEET IS NOT PART OF AND DOES NOT COUNT AS A SHEET OF THE INTERNATIONAL APPLICATION

APPLICANT: Euroceltique S.A.

This column for use by receiving Office

INTERNATIONAL APPLICATION NUMBER (to be filled in by the receiving Office): PCT/US 92/10146

DATE STAMP OF RECEIVING OFFICE: 25 NOV 1992

FEE CALCULATION SHEET[1]

FEES SUBMITTED OR TO BE CHARGED TO DEPOSIT ACCOUNT

I. TRANSMITTAL FEE[2] ..... 200.00 [T] — $200

II. SEARCH FEE[3] ..... 410.00 [S] — 410

International search to be effected by ..... (Please indicate, but only if the applicant has the choice between two or more International Searching Authorities, the name of the Authority to which the international application is to be transmitted. Note that the amount of the search fee depends on the identity of the International Searching Authority.)

III. INTERNATIONAL FEE[4]

BASIC FEE[5]

Indicate the number of SHEETS contained in the international application: 57

first 30 sheets ..... 525.00 [b_1] — 525

remaining 27 sheets × 10.00 = 270.00 [b_2] — 270

Add amounts entered in boxes b_1 and b_2 and enter total in box B. This figure is the amount of the BASIC FEE ..... 795.00 [B] — 795

DESIGNATION FEES[5]

Indicate the number of NATIONAL PATENTS which have been sought and multiply by the amount of the designation fee. 34 × 127 = 4318.00 [d_1]

Indicate the number of REGIONAL PATENTS which have been sought and multiply by the amount of the designation fee. 2 × 127 = 254.00 [d_2]

Add amounts entered in boxes d_1 and d_2 and enter total in box D (if that total exceeds the figure which corresponds to the amount of the designation fee multiplied by ten, enter the latter figure in Box D)[6]. This figure is the amount of the DESIGNATION FEES ..... 1270.00 [D] — 1270

Add amounts entered in boxes B and D, and enter total in box I. This figure is the total amount of the INTERNATIONAL FEE ..... 2065.00 [I] — 12

IV. TOTAL OF PRESCRIBED FEES SUBMITTED OR TO BE CHARGED TO DEPOSIT ACCOUNT

Add amounts entered in boxes T, S and I, and enter total in the TOTAL box. This figure is the amount of the PRESCRIBED FEES SUBMITTED OR TO BE CHARGED TO DEPOSIT ACCOUNT ..... 2675.00 TOTAL — $2,687

THE APPLICANT MAY PAY THE PRESCRIBED FEES BY [CHEQUE, POSTAL MONEY ORDER, BANK DRAFT, CASH, REVENUE STAMPS, COUPONS, ETC.]. PAYMENT SHOULD BE MADE IN THE PRESCRIBED CURRENCY TO THE [ACCOUNT OF, ACCOUNT INDICATED BELOW OF, ORDER OF] THE RECEIVING OFFICE. PAYMENT MAY ALSO BE MADE BY AUTHORIZATION TO CHARGE A DEPOSIT ACCOUNT AT THE RECEIVING OFFICE IF THE LATTER HAS A DEPOSIT ACCOUNT SYSTEM.

DEPOSIT ACCOUNT AUTHORIZATION[7]

☐ The RO/ is hereby authorized to charge the total fees indicated above to my deposit account.

☒ The RO/US is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☒ The RO/US is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

19-4210 — Deposit Account Number

November 25, 1992 — Date

Signature: Clifford M. Davidson

See notes on reverse side

Form PCT/RO/101 (Annex) (January 1991)

(January 1991)

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PCT/US 92/10146

Sheet number 2

Box No. III CONTINUATION (IF REQUIRED) FURTHER APPLICANTS, IF ANY; (FURTHER) INVENTORS, IF ANY; DESIGNATED STATES FOR WHICH THEY ARE APPLICANTS (IF APPLICABLE). A separate sub-box has to be filled in in respect of each person (includes, where applicable, a legal entity).

The person identified in this sub-box is (mark one check-box only): [X] applicant and inventor* [ ] applicant only [X] inventor only*

Name and address:**

MINOGUE, John Joseph
33 East Grand Street, B-2B
Mount Vernon, New York, United States of America 10552

If the person identified in this sub-box is *applicant (or applicant and inventor)*, indicate also:

State of nationality: US State of residence:*** US

and whether that person is *applicant* for the purposes of (mark one check-box only):

[ ] all designated States [ ] all designated States except the United States of America [X] the United States of America only [ ] the States indicated in the "Supplemental Box"

The person identified in this sub-box is (mark one check-box only): [X] applicant and inventor* [ ] applicant only [X] inventor only*

Name and address:**

KAIKO, Robert Francis
10 Norfield Woods Road
Weston, Connecticut, United States of America 06883

If the person identified in this sub-box is *applicant (or applicant and inventor)*, indicate also:

State of nationality: US State of residence:*** US

and whether that person is *applicant* for the purposes of (mark one check-box only):

[ ] all designated States [ ] all designated States except the United States of America [X] the United States of America only [ ] the States indicated in the "Supplemental Box"

The person identified in this sub-box is (mark one check-box only): [ ] applicant and inventor* [ ] applicant only [ ] inventor only*

Name and address:**

If the person identified in this sub-box is *applicant (or applicant and inventor)*, indicate also:

State of nationality: State of residence:***

and whether that person is *applicant* for the purposes of (mark one check-box only):

[ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the "Supplemental Box"

The person identified in this sub-box is (mark one check-box only): [ ] applicant and inventor* [ ] applicant only [ ] inventor only*

Name and address:**

If the person identified in this sub-box is *applicant (or applicant and inventor)*, indicate also:

State of nationality: State of residence:***

and whether that person is *applicant* for the purposes of (mark one check-box only):

[ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the "Supplemental Box"

* If the person indicated as "applicant and inventor" or as "inventor only" is not an *inventor* for the purposes of all the designated States, give the necessary indications in the "Supplemental Box."

** Indicate the name of a natural person by giving his/her family name first (followed by the given name(s). Indicate the name of a legal entity by its full official designation. In the address, include both the postal code (if any) and the State (name).

*** If residence is not indicated, it will be assumed that the State of residence is the same as the State indicated in the address.

If this continuation sheet is not used, it need not be included in the Request.

Form PCT/RO/101 (continuation sheet) (January 1991) See notes on accompanying sheet

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Sheet number 3

Box No. IV AGENT (IF ANY) OR COMMON REPRESENTATIVE (IF ANY); ADDRESS FOR NOTIFICATIONS (IN CERTAIN CASES). A common representative may be appointed only if there are several applicants and if no agent is or has been appointed; the common representative must be one of the applicants.
The following person (includes, where applicable, a legal entity) is hereby/has been appointed as agent or common representative to act on behalf of the applicant(s) before the competent International Authorities:

Name and address, including postal code and country: If the space below is used instead for an address for notifications, mark here: ☐

Harold D. Steinberg, Martin G. Raskin,
Clifford M. Davidson and Brian Roffe of:
STEINBERG AND RASKIN
1140 Avenue of the Americas
New York, New York 10036

Telephone number (including area code): 212-768-3800 Telegraphic address: United States of America Teleprinter address: 212-382-2124

Box No. V DESIGNATION OF GROUPS OF STATES OR STATES(1); CHOICE OF CERTAIN KINDS OF PROTECTION OR TREATMENT. The following designations are hereby made (please mark the applicable check-boxes):

Regional Patent

☒ EP European Patent(2): AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FR France, GB United Kingdom, GR Greece, IT Italy, LU Luxembourg, NL Netherlands, SE Sweden, MC Monaco PT Portugal IE Ireland and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ OA OAPI Patent: Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Gabon, Mali, Mauritania, Senegal, Togo, Cote d'Ivoire and any other State which is a Contracting State of OAPI and of the PCT; if other OAPI title desired, specify on dotted line(3):

National Patent (if other kind of protection or treatment desired, specify on dotted line(3)

☒ AT	Austria(3)	☒ KR	Republic of Korea(3)
☒ AU	Australia(3)	☒ LK	Sri Lanka
☒ BB	Barbados	☒ LU	Luxembourg(3)
☒ BG	Bulgaria(3)	☒ MC	Monaco(3)
☒ BR	Brazil(3)	☒ MG	Madagascar
☒ CA	Canada	☒ MW	Malawi(3)
☒ CH and LI	Switzerland and Liechtenstein	☒ NL	Netherlands
☒ DE	Germany(3)	☒ NO	Norway
☒ DK	Denmark	☒ PL	Poland(3)
☒ ES	Spain(3)	☒ RO	Romania
☒ FI	Finland	☒ SD	Sudan
☒ GB	United Kingdom	☒ SE	Sweden
☒ HU	Hungary	☒ SU	Soviet Union(3) Russian Federation
☒ JP	Japan(3)		
☒ KP	Democratic People's Republic of Korea(3)	☒ US	United States of America(3)

Space reserved for designating States (for the purposes of a national patent) which have become party to the PCT after the issuance of this sheet:

Additional EP countries: All countries currently members of the EPO including Ireland, Portugal IE PT

Mongolia, Czechoslovakia, Cote d'Ivoire MN CS

(1) The applicant's choice of the order of designations may be indicated by marking the check-boxes with sequential arabic numerals (see also the "Notes to Box No. V").
(2) The selection of particular States for a European patent can be made upon entering the national (regional) phase before the European Patent Office (see also the "Notes to Box No. V").
(3) If another kind of protection or a title of addition or, in the United States of America, treatment as a continuation or a continuation-in-part is desired, specify according to the instructions given in the "Notes to Box No. V."

Form PCT/RO/101 (second sheet) (January 1991) See notes on accompanying sheet

DELETED RO/US RC 5 Surname underlined By RO/US

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PCT/ : 92/10115

Sheet number 4

Box No. VI PRIORITY CLAIM (IF ANY). The priority of the following earlier application(s) is hereby claimed:

Country (country in which it was filed if national application; one of the countries for which it was filed if regional or international application)	Filing Date (day, month, year)	Application No.	Office of filing (fill in only if the earlier application is an international application or a regional application)
(1) United States of America	27 November 1991 (27/11/91) (27.11.91)	07/800,549	
(2)			
(3)			

(Letter codes may be used to indicate country and/or Office of filing)

When the earlier application was filed with the Office which, for the purposes of the present international application, is the receiving Office, the applicant may, against payment of the required fee, ask the following:

☒ the receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the above-mentioned earlier application/of the earlier applications identified above by the numbers (insert the applicable numbers): .....

Box No. VII EARLIER SEARCH (IF ANY). Fill in where a search (international, international-type or other) by the International Searching Authority has already been requested (or completed) and the said Authority is now requested to base the international search, to the extent possible, on the results of the said earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request.

International application number or number and country (or regional Office) of other application: United States of America 07/800,549

Date of request for search:

International/regional/national filing date: 27 November 1991 (27.11.91)

Number (if available) given to search request:

Box No. VIII SIGNATURE OF APPLICANT(S) OR AGENT

Clifford M. Davidson

Clifford M. Davidson

If the present Request form is signed on behalf of any applicant by an agent, a separate power of attorney appointing the agent and signed by the applicant is required. If in such case it is desired to make use of a general power of attorney (deposited with the receiving Office), a copy thereof must be attached to this form.

Box No. IX CHECK LIST (To be filled in by the Applicant)

This international application contains the following number of sheets:

1. request	4	sheets
2. description	41	sheets
3. claims	6	sheets
4. abstract	1	sheets
5. drawings	5	sheets
Total	57	sheets

Figure number ..... of the drawings (if any) is suggested to accompany the abstract for publication.

This international application as filed is accompanied by the items marked below:

1. ☒ separate signed power of attorney Unsigned
2. ☐ copy of general power of attorney
3. ☐ priority document(s) (see Box No. VI)
4. ☐ receipt of the fees paid or revenue stamps
5. ☒ cheque for the payment of fees
6. ☒ request to charge deposit account
7. ☐ other document (specify)

(The following is to be filled in by the receiving Office)

1. Date of actual receipt of the purported international application: 13 Rec'd PCT/PTO 25 NOV 1992
2. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
3. Date of timely receipt of the required corrections under Article 11 of the PCT:
4. Drawings ☐ Received ☐ No Drawings

(The following is to be filled in by the International Bureau)

Date of receipt of the record copy:

Form PCT/RO/101 (last sheet) (January 1991) See notes on accompanying sheet

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PATENT COOPERATION TREATY

From the RECEIVING OFFICE

To:

HAROLD D. STEINBERG
STEINBERG & RASKIN
1140 AVENUE OF THE AMERICAS
NEW YORK, NEW YORK 10036

PCT

NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

Date of mailing (day/month/year)	24 DEC 1992
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
92-515	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US92/10146	25 NOV 92	27 NOV 91

Applicant EUROCELTIQUE S.A.

Title of the invention CONTROLLED RELEASE OXYCODONE COMPOSITIONS

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:

☒ was transmitted to the International Bureau on 24 DEC 1992.

☐ has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau*:

☐ because the necessary national security clearance has not yet been obtained.

☐ because *(reason to be specified)*:

NO LICENSE CURRENTLY REQUIRED
FOR FOREIGN TRANSMITTAL OF THIS SUBJECT MATTER.
37 CFR 5.11(e) and/or 37 CFR 5.12 (a)

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

Name and mailing address of the receiving Office	Authorized officer
COMMISSIONER OF PATENTS AND TRADEMARKS Box PCT Washington, D.C. 20231 Attn: RO/US	
Facsimile No.	Telephone No.

Form PCT/RO/105 (July 1992)

MARK A. ROGARTH
INTERNATIONAL DIVISION

PCT/US92/10

'ATENT COOPERATION TRE. Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

STEINBERG, Harold, D.
Steinberg and Raskin
1140 Avenue of the Americas
New York, NY 10036
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing: 30 December 1992 (30.12.92)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference: 92-515	International application No.: PCT/US92/10146

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

EUROCELTIQUE S.A. (for all designated States except US)
OSHLACK, Benjamin et al (for US)

International filing date	:	25 November 1992 (25.11.92)
Priority date(s) claimed	:	27 November 1991 (27.11.91)
Date of receipt of the record copy by the International Bureau	:	28 December 1992 (28.12.92)
Designated Offices which will be notified of the receipt of the record copy	:	AT,AU,BB,BG,BR,CA,CH,CS,DE,DK,EP*,ES,FI,GB,HU, JP,KP,KR,LK,LU,MG,MN,MW,NL,NO,OA,PL,PT,RO,RU, SD,SE,US * AT,BE,CH,DE,DK,ES,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase;
- [ ] confirmation of precautionary designations;
- [ ] requirements regarding priority documents.

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorised officer: J. Leitao
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 730.91.11

Form PCT/IB/301 (July 1992) 000110556

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L.C.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/081,302	06/18/93	OSHLACK	B 93311

WEBMAN, E EXAMINER

15M1/0411

STEINBERG & RASKIN
1140 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

ART UNIT	PAPER NUMBER
1502	4

DATE MAILED: 04/11/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire ~~3~~ month(s), 30 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1 – 11 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☐ Claims _____ are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1 – 11 are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-2, drawn to method, classified in Class 514, subclass 282.

II. Claims 3-11, drawn to composition, classified in Class 424, subclass 464.

The inventions are distinct, each from the other because of the following reasons:

Inventions II and I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the process as claimed can be practiced with another materially different product such as an injectable gel.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Should group II be elected, the following election of one of species a)-d) rejected below is required.

This application contains claims directed to the following patentably distinct species of the claimed invention:

a) the composition of claims 3, 4

b) the composition of claims 5, 6

c) the composition of claims 7, 8

d) the composition of claims 9, 10 and 11.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, a solid oral dosage form is generic.

Applicant is advised that a response to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. M.P.E.P. § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the

case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Edward J. Webman whose telephone number is (703) 308-4432.

EDWARD J. WEBMAN
PRIMARY EXAMINER
GROUP 1500

Edward J. Webman:cb
April 6, 1994

1502

EAP 05/25/94

93-311

UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: E. Webman Art Unit: 1502

Re: Application of: Benjamin OSHLACK, et al.

Serial No.: 08/081,302

Filed: June 18, 1993

For: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

RESPONSE TO RESTRICTION REQUIREMENT

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

May 11, 1994

Sir:

In response to the Restriction Requirement dated April 11, 1994, applicants hereby elect to prosecute Group II (claims 3-11), drawn to the composition, classified in Class 424, Subclass 464.

In the Restriction Requirement, the Examiner further required an election of one of species (a)-(d). Applicants hereby elect the "species" (d), in other words, the composition of claims 9, 10 and 11. This election is also made with traverse.

I hereby certify that this correspondence and/or fee is being deposited with the United States Postal Service as first class mail in an envelope addressed to "Commissioner of Patents and Trademarks, Washington, DC 20231" on May 11, 1994.

STEINBERG, RASKIN & DAVIDSON

BY: _____

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With regard to the Restriction Requirement, the Examiner states that inventions of Groups I (claims 1-2 drawn to the method) and II (claims 3-11 drawn to the composition) are distinct because "in the instant case the process as claimed can be practiced with another material different product such as an injectable gel".

In this case, it is respectfully submitted that the Examiner has failed to recognize the fact that claims 1 and 2 both specify that the method is related to administering an oral controlled release dosage formulation. Further, the composition of Group II are also only for oral administration. Therefore, to state that the process can be practiced with a materially different product as an injectable gel is simply not understood. In view of this fact, it is respectfully submitted that the restriction requirement has been overcome and should now be removed.

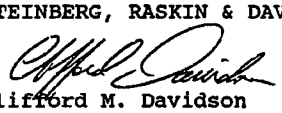
The Examiner's requirement of an election is also not understood. The subject matter of claims 3-11 is a controlled release oxycodone formulation which provides specified mean maximum plasma concentrations and mean minimum plasma concentrations for a given dosage range at a given range of time periods. It is not understood why an election is necessary. In view of this fact, the Examiner's election requirement is also traversed and it is requested that the Examiner remove this requirement.

An early and favorable action on the merits is earnestly solicited.

If the Examiner would consider it beneficial to further discuss any aspect of this response or of the restriction requirement, then the Examiner is invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

STEINBERG, RASKIN & DAVIDSON



Clifford M. Davidson

STEINBERG, RASKIN & DAVIDSON
1140 Avenue of the Americas
New York, New York 10036
(212) 768-3800

CMD/PF/93-311/RESTREQ.M11

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/081,302	06/18/93	OSHLACK	B 93311

WEBMAN, E EXAMINER

ART UNIT	PAPER NUMBER
1502	6

DATE MAILED: 08/22/94

10.

15M1/0822

STEINBERG & RASKIN
1140 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☒ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ___ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-11 are pending in the application.
   Of the above, claims 1-8 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 9-11 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

'912 - 114

Applicant's election with traverse of claims 9, 10, 11 in Paper No. 5 is acknowledged. The traversal is on the ground(s) that the method requires oral administration. This is not found persuasive because the method of use is to reduce pain, not necessarily by oral administration. The election is over various species of formulations: an unspecified formulation, e.g., a solution, an unspecified solid, a coated spheroid, and a table.

The requirement is still deemed proper and is therefore made FINAL.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> 35 U.S.C. § 101 reads as follows:
> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 9-11 are rejected under 35 U.S.C. § 102(b) as being anticipated by 4,990,341.

Applicants disclose that 4,990,341 teaches opoid analgesics with the claimed rate of release (page 2, lines 8-20). Tables are disclosed (example 1 in '341).

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Edward J. Webman whose telephone number is (703) 308-4432.

Webman:css
August 20, 1994

EDWARD J. WEBMAN
PRIMARY EXAMINER
GROUP 1500

Form PTO 948 (Rev. 10-93) U.S. DEPARTMENT OF COMMERCE - Patent and Trademark Office Application No. 08/302

NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

PTO Draftpersons review all originally filed drawings regardless of whether they are designated as formal or informal. Additionally, patent Examiners will review the drawings for compliance with the regulations. Direct telephone inquiries concerning this review to the Drawing Review Branch, 703-305-8404.

The drawings filed (insert date) 6/8/93, are
A. ✓ not objected to by the Draftsperson under 37 CFR 1.84 or 1.152.
B. ____ objected to by the Draftsperson under 37 CFR 1.84 or 1.152 as indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawings must be submitted according to the instructions on the back of this Notice.

1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings:
Black ink. Color.
___ Not black solid lines. Fig(s)____
___ Color drawings are not acceptable until petition is granted.

2. PHOTOGRAPHS. 37 CFR 1.84(b)
___ Photographs are not acceptable until petition is granted.

3. GRAPHIC FORMS. 37 CFR 1.84 (d)
___ Chemical or mathematical formula not labeled as separate figure. Fig(s)____
___ Group of waveforms not presented as a single figure, using common vertical axis with time extending along horizontal axis. Fig(s)____
___ Individuals waveform not identified with a separate letter designation adjacent to the vertical axis. Fig(s)____

4. TYPE OF PAPER. 37 CFR 1.84(e)
___ Paper not flexible, strong, white, smooth, nonshiny, and durable. Sheet(s)____
___ Erasures, alterations, overwritings, interlineations, cracks, creases, and folds not allowed. Sheet(s)____

5. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable paper sizes:
21.6 cm. by 35.6 cm. (8 1/2 by 14 inches)
21.6 cm. by 33.1 cm. (8 1/2 by 13 inches)
21.6 cm. by 27.9 cm. (8 1/2 by 11 inches)
21.0 cm. by 29.7 cm. (DIN size A4)
___ All drawing sheets not the same size. Sheet(s)____
___ Drawing sheet not an acceptable size. Sheet(s) ____

6. MARGINS. 37 CFR 1.84(g): Acceptable margins:

	Paper size			
	21.6 cm. X 35.6 cm. (8 1/2 X 14 inches)	21.6 cm X 33.1 cm. (8 1/2 X 13 inches)	21 cm. X 27.9 cm. (8 1/2 X 11 inches)	21 cm. X 29.7 cm. (DIN Size A4)
T	5.1 cm. (2")	2.5 cm. (1")	2.5 cm. (1")	2.5cm.
L	.64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	2.5 cm.
R	.64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	1.5 cm.
B	.64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	1.0 cm.

Margins do not conform to chart above.
Sheet(s)____
___Top (T) ___ Left (L) ___Right (R) ___Bottom (B)

7. VIEWS. 37 CFR 1.84(h)
REMINDER: Specification may require revision to correspond to drawing changes.
___ All views not grouped together. Fig(s)____
___ Views connected by projection lines. Fig(s)____
___ Views contain center lines. Fig(s)____
Partial views. 37 CFR 1.84(h)(2)
___ Separate sheets not linked edge to edge. Fig(s)____
___ View and enlarged view not labeled separately. Fig(s)____
___ Long view relationship between different parts not clear and unambiguous. 37 CFR 1.84(h)(2)(ii) Fig(s)____
Sectional views. 37 CFR 1.84(h)(3)
___ Hatching not indicated for sectional portions of an object. Fig(s)____
___ Hatching of regularly spaced oblique parallel lines not spaced sufficiently. Fig(s)____
___ Hatching not at substantial angle to surrounding axes or principal lines. Fig(s)____
___ Cross section not drawn same as view with parts in cross section with regularly spaced parallel oblique strokes. Fig(s)____
___ Hatching of juxtaposed different elements not angled in a different way. Fig(s)____
Alternate position. 37 CFR 1.84(h)(4)
___ A separate view required for a moved position. Fig(s)____

Modified forms. 37 CFR 1.84(h)(5)
___ Modified forms of construction must be shown in separate views. Fig(s)____

8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)
___ View placed upon another view or within outline of another. Fig(s)____
___ Words do not appear in a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s)____

9. SCALE. 37 CFR 1.84(k)
___ Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction. Fig(s)____
___ Indication such as "actual size" or "scale 1/2" not permitted. Fig(s)____
___ Elements of same view not in proportion to each other. Fig(s)____

10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(l)
___ Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (except for color drawings). Fig(s)____

11. SHADING. 37 CFR 1.84(m)
___ Shading used for other than shape of spherical, cylindrical, and conical elements of an object, or for flat parts. Fig(s)____
___ Solid black shading areas not permitted. Fig(s)____

12. NUMBERS, LETTERS, & REFERENCE CHARACTERS. 37 CFR 1.84(p)
___ Numbers and reference characters not plain and legible. 37 CFR 1.84(p)(1) Fig(s)____
___ Numbers and reference characters used in conjuction with brackets, inverted commas, or enclosed within outlines. 37 CFR 1.84(p)(1) Fig(s)____
___ Numbers and reference characters not oriented in same direction as the view. 37 CFR 1.84(p)(1) Fig(s)____
___ English alphabet not used. 37 CFR 1.84(p)(2) Fig(s)____
___ Numbers, letters, and reference characters do not measure at least .32 cm. (1/8 inch) in height. 37 CFR(p)(3) Fig(s)____

13. LEAD LINES. 37 CFR 1.84(q)
___ Lead lines cross each other. Fig(s)____
___ Lead lines missing. Fig(s)____
___ Lead lines not as short as possible. Fig(s)____

14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t)
___ Number appears in top margin. Fig(s)____
___ Number not larger than reference characters. Fig(s)____
___ Sheets not numbered consecutively, and in Arabic numerals, beginning with number 1. Sheet(s)____

15. NUMBER OF VIEWS. 37 CFR 1.84(u)
___ Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s)____
___ View numbers not preceded by the abbreviation Fig. Fig(s)____
___ Single view contains a view number and the abbreviation Fig.
___ Numbers not larger than reference characters. Fig(s)____

16. CORRECTIONS. 37 CFR 1.84(w)
___ Corrections not durable and permanent. Fig(s)____

17. DESIGN DRAWING. 37 CFR 1.152
___ Surface shading shown not appropriate. Fig(s)____
___ Solid black shading not used for color contrast. Fig(s)____

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FORM PTO-1083

Docket No. 93-311
Date: February 22, 1995

In re application of: Benjamin OSHLACK, et al.
Serial No.: 08/081,302
Filed: June 18, 1993
For: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

THE COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, DC 20231

Sir:
Transmitted herewith is an Amendment in the above-identified application.

MAR 1 4 1995

[ ] Small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a verified statement previously submitted.
[ ] A verified statement to establish small entity status under 37 CFR 1.9 and 1.27 is enclosed.
[X] No fee for additional claims is required.
[ ] A filing fee for additional claims calculated as shown below, is required:

	(Col. 1)	(Col. 2)		SMALL ENTITY		OR	LARGE ENTITY	
FOR:	REMAINING AFTER AMENDMENT	HIGHEST PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	FEE		RATE	FEE
TOTAL CLAIMS	* 3	Minus** 20=	0	x $ 11	$		x $ 22	$ 0
INDEP. CLAIMS	* 1	Minus*** 3=	0	x $ 38	$		x $ 76	$ 0
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				+ $120	$		+ $240	$
				TOTAL:	$	OR	TOTAL:	$-0-

* If the entry in Co. 1 is less than the entry in Col. 2, write "0" in Col. 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

[X] Also transmitted herewith are:
[X] Petition for extension under 37 CFR 1.136 (in duplicate)
[ ] Other:

[ ] Please charge my Deposit Account No. 19-4210 in the amount of _____. A duplicate copy of this sheet is enclosed.

[X] A check in the amount of $870.00 is attached to cover:
[ ] Filing fee for additional claims under 37 CFR 1.16
[X] Petition fee for extension under 37 CFR 1.136
[ ] Other:

[X] The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 19-4210. A duplicate copy of this sheet is enclosed.

[X] Any filing fee under 37 CFR 1.16 for the presentation of additional claims which are not paid by check submitted herewith.
[ ] Any patent application processing fees under 37 CFR 1.17.
[X] Any petition fees for extension under 37 CFR 1.136 which are not paid by check submitted herewith, and it is hereby requested that this be a petition for an automatic extension of time under 37 CFR 1.136.

Clifford M. Davidson
Reg. No. 32,728
STEINBERG, RASKIN AND DAVIDSON P.C.
1140 Avenue of the Americas
New York, New York 10036
(212) 768-3800

I hereby certify that this correspondence and/or fee is being deposited with the United States Postal Service as first class mail in an envelope addressed to: "Commissioner of Patents and Trademarks, Washington, DC 20231" on February 22, 1995.

STEINBERG, RASKIN AND DAVIDSON P.C.

By: _____

'912 - 118

15 Webman 870 — 117 150

93-311

UNITED STATES PATENT AND TRADEMARK OFFICE

#7/W.M 3/24/

MAR 14 1995

Examiner: E. Webman Art Unit: 1502

Re: Application of: Benjamin OSHLACK, et al.

Serial No.: 08/081,302

Filed: June 18, 1993

For: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

PETITION FOR EXTENSION UNDER 37 CFR 1.136(a)

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

February 22, 1995

Sir:

Applicants hereby petition the Commissioner of Patents and Trademarks to extend the time for response to the Office Action dated August 22, 1994 for three months from November 22, 1994 to February 22, 1995.

Submitted herewith is a check for $870.00 to cover the cost of the extension.

Any deficiency or overpayment should be charged or credited to Deposit Account No. 19-4210. A duplicate copy of this sheet is enclosed.

Respectfully Submitted,
STEINBERG, RASKIN & DAVIDSON, P.C.

By: _____
Clifford M. Davidson
Reg. No. 32,728

Steinberg, Raskin & Davidson, P.C.
1140 Avenue of the Americas
New York, N.Y. 10036
(212) 768-3800

I hereby certify that this correspondence and/or fee is being deposited with the United States Postal Service as first class mail in an envelope addressed to "Commissioner of Patents and Trademarks Washington, D.C. 20231" on February 22, 1995.
STEINBERG, RASKIN & DAVIDSON, P.C.

BY: _____

93-311

UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: E. Webman Art Unit: 1502

Re: Application of: Benjamin OSHLACK, et al.

Serial No.: 08/081,302

Filed: June 18, 1993

For: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

AMENDMENT

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

February 22, 1995

Sir:

In response to the Office Action dated August 22, 1994, Applicants submit the following remarks:

REMARKS

Reconsideration of the present application is respectfully requested.

I. The Restriction Requirement

In the Office Action dated August 22, 1994, the Examiner has acknowledged Applicants' election of claims 9-11 with traverse and made the restriction requirement final, removing claims 1-8 from further consideration. Applicants respectfully reserve the